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Stereoselective S_E2' Protonation of α-Hydroxyallylsilanes Mediated by a Brook Rearrangement

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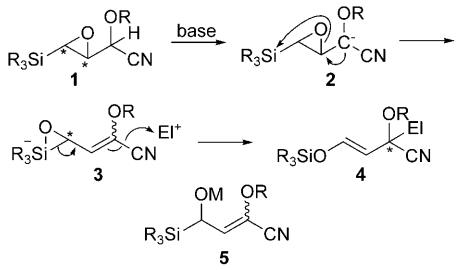
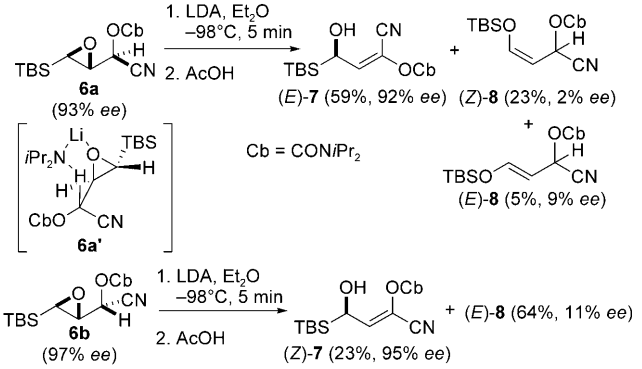
We have recently reported that enantioselective C–C bond formation at an α-position of a cyano group with an external electrophile (**1**→**2**→**3**→**4**; Scheme 1) can be realized, although in modest enantiomeric excess (*ee*), with the aid of both the concerted process of epoxysilane rearrangement and a carbamoyl group (R = Cb).[1] During the course of stereochemical studies of the reaction, we attempted to trap α-silyl alkoxide derivatives **5** (M = Li), possible intermediates in the reaction pathway, as alcohols **5** (M = H) by quenching the reaction at lower temperatures, with the expectation that isolation of the alcohol would allow us to obtain useful information regarding the stereochemical pathway of the S_E2' reaction in allylsilicates such as **3**. To the best of our knowledge, there is no precedent for a stereochemical discussion concerning S_E2' reaction in allylsilicates, derived from allylsilanes with an oxygen substituent on the stereogenic center, as in **3**, by means of a Brook rearrangement,[2,3] in sharp contrast to the extensive body of knowledge concerning the corresponding reactions of allylsilanes.[4]



Scheme 1. Chirality transfer in epoxysilane rearrangement.

After extensive experimentation, it proved possible to isolate **5** (M = H) by performing the reaction in Et_2O at a lower temperature.[5] Thus, treatment of **6a**[1] with LDA at −98 °C in Et_2O afforded (*E*)-**7** in 59% yield together with (*E*)- and (*Z*)-**8** (Scheme 2). A similar result was obtained



Scheme 2. Preparation of (*E*)- and (*Z*)-**7**.

with **6b**[1] to give (*Z*)-**7**. The observed stereospecificity was consistent with a *syn*-attack ring-opening (e.g., **6a′**) of the epoxide, although we have suggested an *anti*-attack ring-opening for similar reactions using the corresponding OTBS derivatives in THF.[6,7] The geometry of **7** was determined on the basis of result of X-ray analysis of (*Z*)-**7**.

With the desired alcohol derivatives (*E*)- and (*Z*)-**7** in hand, we examined their benzylation by exposure to LDA in the presence of BnBr (Scheme 3). When LDA was added to a solution of (*E*)-**7** in Et_2O at −80 °C in the presence of BnBr and the reaction was quenched after 1 h, (*Z*)- and (*E*)-**9** were obtained in 85% and 8% yields, respectively, to-

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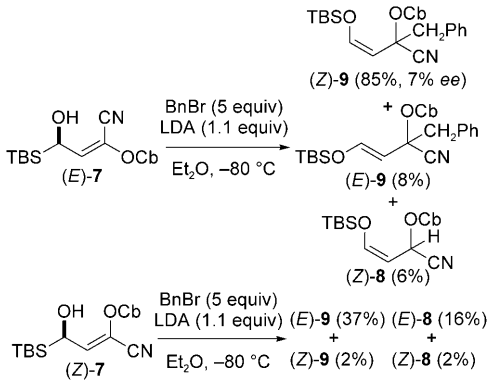
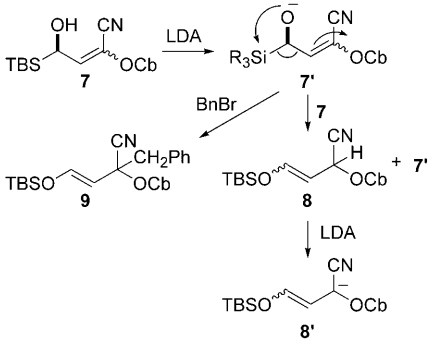


Scheme 3. Reaction of (*E*)- and (*Z*)-**7** with LDA in the presence of benzyl bromide.

gether with protonated product (*Z*)-**8**. In contrast to the results obtained in the reaction of **6a** (30–40% *ee*),[1] the *ee*'s of almost all products were low. Reaction of (*Z*)-**7** provided (*E*)- and (*Z*)-**9** with low *ee* in a reversed ratio.

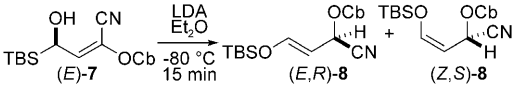
We attributed the loss of enantiomeric excess in the products to the result of competition between benzylation and C-protonation by **7** in α-silyl alkoxide **7′**; the latter process leading to **8** should be much faster than the former (Scheme 4). Compound **8** can be racemized to give the α-nitrile carbanion **8′** by deprotonation with LDA even if the protonation of **7′** by **7** (**7′**→**8**) proceeds stereoselectively by a concerted process.



Scheme 4. A plausible pathway of racemization in the reactions in Scheme 3.

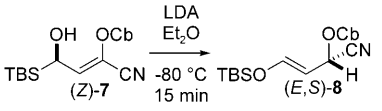
If this explanation is correct, use of a catalytic amount of LDA should give **8** in increased enantioselectivity, because the hydroxyl group in **7** can be a proton source and minimize the formation of **8′** by LDA. The results are shown in Tables 1 and 2. As expected, the enantiomeric excess increased with decreasing amount of LDA in the reactions of both (*E*)-and (*Z*)-**7**; thus, use of 0.1 equiv and 1.0 equiv of LDA gave the best and poorest results in terms of *ee*, respectively, and with regard to chemical yield the best result was obtained when 0.3 equiv of the base was used. The lower chemical yields when using stoichiometric amounts of the base may stem from base-induced decomposition in **8**.

Table 1. Reaction of (*E*)-**7** with LDA.



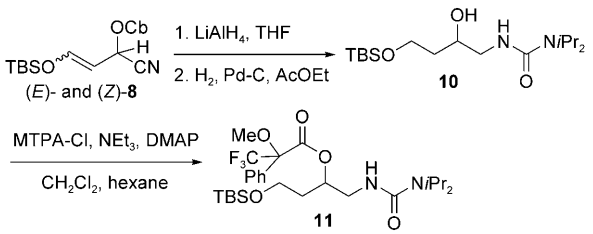
LDA	(*E*,*R*)-**8**		(*Z*,*S*)-**8**		(*E*)-**7**
[equiv]	Yield [%]	*ee* [%]	Yield [%]	*ee* [%]	Yield [%]
0.1	5	69	4	35	33
0.3	20	29	34	9	–
0.6	13	25	32	8	–
1.0	7	0	38	0	–

Table 2. Reaction of (*Z*)-**7** with LDA.



LDA	(*E*,*S*)-**8**		(*Z*)-**7**
[equiv]	Yield [%]	*ee* [%]	Yield [%]
0.1	54	68	25
0.3	77	55	–
0.6	78	38	–
1.0	18	4	13

The absolute configurations of the major enantiomer (*E*)- and (*Z*)-**8** were determined as shown in Scheme 5 after derivatization of (*E*)- and (*Z*)-**8** separately to the Mosher esters

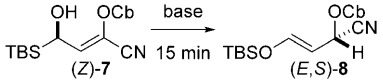


Scheme 5. Determination of absolute configurations of (*E*,*Z*)-**8**.

11[8] through the reduction of the nitrile group followed by an O-to-N migration[1] of the carbamoyl group. It should be noted that the stereogenic centers of the major enantiomers of (*E*)- and (*Z*)-**8** obtained from (*E*)-**7** were enantiomeric with each other and the stereogenic center of (*E*)-**8** obtained from (*E*)-**7** was enantiomeric with that of (*E*)-**8** from (*Z*)-**7**.

Next we examined the effects of the solvent and base on enantioselectivity using (*Z*)-**7** (Table 3). Addition of hexane resulted in enhancement of *ee* at the expense of chemical yield (entries 1 and 2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and LiO*t*Bu (entries 3–8) were used with anticipation that as they are less basic, the deprotonation of **8** can be suppressed and the generation of a conjugate acid of DBU and of *t*BuOH can accelerate the protonation of the α-nitrile carbanion. Although use of DBU in DMSO resulted in significant decomposition, reactions using LiO*t*Bu pro-

Table 3. Reaction of (*Z*)-**7** with a catalytic amount of base.

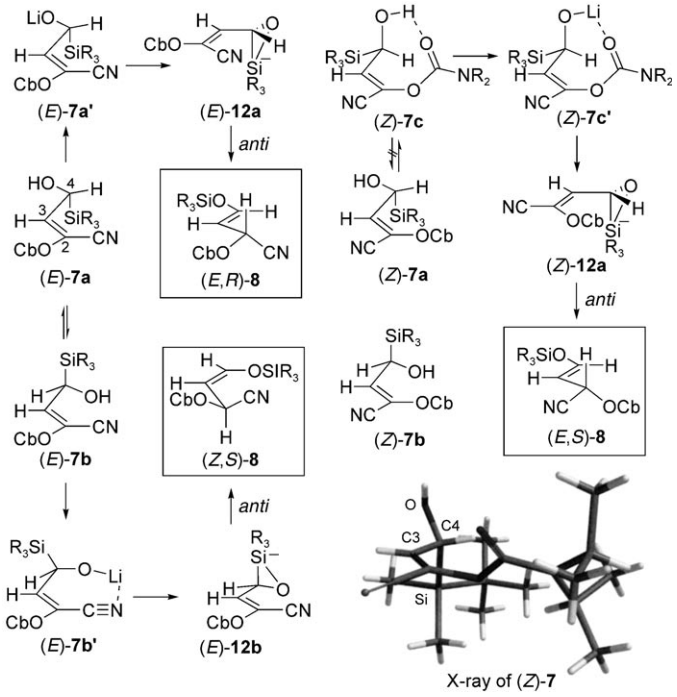


Entry	Base (equiv)	Solvent	*T* [°C]	(*Z*,*S*)-**8** Yield [%]	*ee* [%]	(*Z*)-**7** Yield [%]
1	LDA (0.1)	Et_2O–hexane (1:1)	−80	20	77	72
2	LDA (0.1)	Et_2O–hexane (1:2)	−80	25	77	56
3	DBU (0.1)	DMSO	RT	14	74	10
4	*t*BuOLi (0.1)	Et_2O	−80	25	61	64
5	*t*BuOLi (0.1)	Et_2O–hexane (1:1)	−80	36	76	50
6	*t*BuOLi (0.1)	Et_2O–hexane (1:1)	0	64	70	20
7	*t*BuOLi (0.1)	Et_2O–hexane (1:1)	RT	85	52	–
8	*t*BuOLi (0.05)	*t*BuOH	RT	86	75	–

vided comparable *ee* values and much better chemical yields than those in the case of LDA in Et_2O/hexane (entries 6–8).

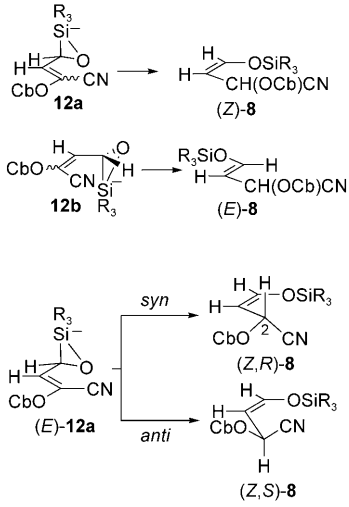
To understand the stereochemical outcome in the reactions of (*E*,*Z*)-**7**, the origin of the stereospecificity depending on the *E*/*Z* geometry of **7** should be rationalized. The *E*/*Z* geometry in **8** would be solely controlled by the conformation of silicate intermediates **12**, which are generated by deprotonation by a base, assuming that no *E*/*Z* isomerization occurs in the products **8** under the conditions used and that C–Si bond cleavage in the silicates occurs in a concerted fashion, while keeping a parallel alignment between the C–Si bond and the π orbital. Thus, conformers **12a** and **12b** give (*Z*)-**8** and (*E*)-**8**, respectively (Scheme 6). On the other hand, the stereochemistry at the C2 position would be regulated by both the double bond geometry and a *syn*/*anti* mode protonation to the C–Si bond in **12**. For example, (*E*)-**12a** would afford (*Z*,*R*)-**8** and (*Z*,*S*)-**8** in *syn* and *anti* forms, respectively.

Consequently, it is important to know in which conformation (*E*)- and (*Z*)-**7** react to give which silicates. This led us to search for stable ground-state conformations of silyl alcohols **7** and lithium alkoxide **7′** by means of the Hartree–Fock calculations (Scheme 7). The two local minima (*E*)-**7a**,**b** for (*E*)-**7** were identified by subjection of conformers that were located by both MMFF94s and Conflex methods



Scheme 7. Stereochemical pathways for reactions of (*E*)- and (*Z*)-**7**.

to geometry optimization at HF/6-31+G* level and then refinement at RI-MP2/6-31+G* level; the former was found to be more stable.[9] In both conformers, the silyl group is aligned almost perpendicularly to the plane of the olefin. In the case of lithium alkoxide, the conformations obtained were similar to those of the alcohol, but the stability was reversed. Thus, an internally chelated conformation (*E*)-**7b′** was found to be more stable than (*E*)-**7a′**. In the case of the *Z* derivatives, only alcohol conformers (*Z*)-**7c** in which the hydroxyl group was almost perpendicular to the plane of the olefin and formed intramolecular hydrogen bonding to the carbonyl group was found. Both (*Z*)-**7a**, which is similar to that obtained from X-ray analysis of (*Z*)-**7**, and a conformer corresponding to (*Z*)-**7b** were not found. In the case of the lithium alkoxide *Z* derivatives, a local minimum identified was only (*Z*)-**7c′**, in which the lithium ion was chelated with the carbonyl oxygen. On the basis of this analysis and the absolute configuration of the products **8**, there is a possible explanation for the results shown in Tables 1 and 2. Thus, (*E*)-**7** affords (*E*,*R*)-**8** and (*Z*,*S*)-**8** through *anti*-attack protonation of silicate intermediates (*E*)-**12a** and (*E*)-**12b** derived from (*E*)-**7a′** and (*E*)-**7b′**, respectively, according to the least motion principle,[10] while (*Z*)-**7** gives only (*E*,*S*)-**8** via (*Z*)-**12a** derived from (*Z*)-**7c′**. The origin for the observed *anti*-attack protonation might be related to steric effects of the bulky silyl group, to steroelectronic effects in the con-



Scheme 6. Stereochemical pathways for the formation of (*Z*)- and (*E*)-**8** and for (*Z*,*R*)- and (*Z*,*S*)-**8**.

certed process involving Brook rearrangement and protonation, and to electronic effects of the carbamoyloxy group. In any case, the interesting results are the subject of more detailed investigations.

In conclusion, we have demonstrated that the S_E2' protonation in allylsilanes, with an oxygen substituent on the stereogenic center, mediated by a Brook rearrangement, in which the resulting allylic carbanion is potentially planarized by a neighboring CN group, proceeds in an *anti* fashion to afford enantiomerically enriched nitrile derivatives. This means that the overall process is equivalent to trapping of an enantioenriched C-chiral α-nitrile carbanion, which has a very low inversion barrier,[11,12] in up to 77% *ee* with the aid of both the concerted process of the protonation and a carbamoyl group.[13]

Experimental Section

A solution of *t*BuOLi (0.5 M in *t*BuOH, 14.8 μL, 0.0074 mmol) was added to a solution of (*Z*)-**7** (50.4 mg, 0.148 mmol) in *t*BuOH (1.7 mL) at 25 °C. The mixture was stirred at the same temperature for 15 min before addition of CH_3COOH (1.0 M in Et_2O, 15 μL, 0.015 mmol). After being stirred at the same temperature for 5 min, the reaction mixture was diluted with 10% aqueous NH_4Cl solution (5 mL) and extracted with Et_2O (5 mL × 3). Combined organic phases were washed with water (5 mL) and saturated brine (5 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 8 g, elution with hexane: Et_2O = 6:1) to give (*E*)-**8** (43.1 mg, 86%, 75% *ee*).

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Keywords: asymmetric synthesis · carbanions · chirality · enantioselectivity · silicates

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